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Chiral N^{β}-Fmoc-amino alkyl isonitriles in Ugi-4CR: an assembly of novel 1,1′-iminodicarboxylated peptidomimetics

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ABSTRACT

Enantiopure N^{β}-Fmoc-amino alkyl isonitriles and amino acid esters have been employed as building blocks in Ugi four-component reaction (U-4CR) to yield 1,1′-iminodicarboxylated peptidomimetics. By employing trifluoroacetic acid as one of the components, a different outcome has been observed and rationalized. Ugi products are obtained as trifluoroacetamide adducts, which on further reaction under mild acidic conditions lead to the title compounds. The method has also been proven to be useful for the preparation of ethyl, benzyl and *tert*-butyl esters.

1. Introduction

The isonitrile based MCRs were developed by Passerini (3CR) in 1921 and then by Ugi (4CR) in 1959.[1] Isonitriles have divalent nature and their unique reactivity provides *C*-nucleophiles toward imines, resulting in nitrilium electrophiles, enables the wide applications of Passerini and Ugi reactions to produce diverse array of products in combinatorial chemistry.[2] Ugi reaction has been the widely recognized MCR, since it has larger flexibility toward generation of small molecules to larger ones, natural products, peptides, heterocycles and other biologically relevant compounds.[3] In Ugi-4CR, an amine, an aldehyde, an isonitrile, and an acid react in one-pot leading to the synthesis of a linear peptide-like adduct. Thus, enantiopure isocyano esters[4] have been synthesized and employed as one of the components in several of the MCRs.[5] They have been employed for the synthesis of complex peptides and peptidomimetics in one-pot.[6] Amino acid derived isocyano ester **1a** remains a focus of much attention, because permutation and combination of new variants would generate a wide variety of novel type of molecules as desired by the pharmaceutical industry.[7] In this context, the use of *C*-terminal modified '*N*-protected amino alkyl isonitriles' **1b** as building blocks in multicomponent reactions would be of considerable interest in order to obtain various peptide-like adducts. A thorough literature survey revealed that only one derivative namely *N*-Fmoc/Boc-amino ethyl isonitrile had been synthesized starting from ethylene diamine in a multistep approach.[8] The above isonitrile was employed for one-pot synthesis of peptide nucleic acids (PNAs). With the objective to incorporate isonitrile functionality in place of carboxy group of optically pure amino acids, we have developed a simple protocol for conversion of carboxylic acid to formamide, followed by dehydration to the isocyanide using Burgess reagent (Fig. 1).[9]

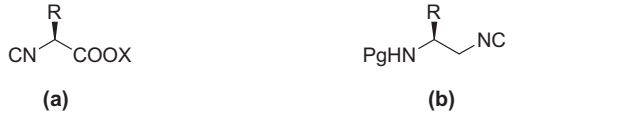

Fig. 1. Amino acid derived isonitriles.

Apart from the application of isocyano ester **1a**, several studies have also been made to broaden the scope of enantiopure bifunctional amino acids/peptides in MCRs.[10] Thus, varieties of biologically active peptidomimetics have been synthesized via Ugi MCRs by using amino acid derivatives as aldehyde,[11] amine[12] or acid component.[13] A prominent example for this kind of MCRs is

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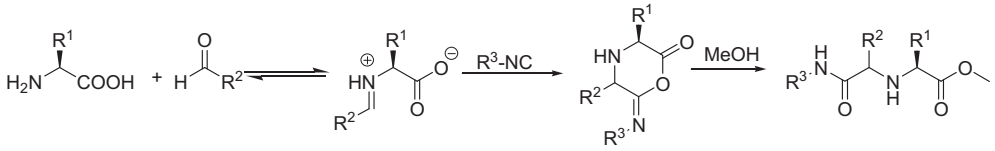
the condensation of amino acid, isonitrile and aldehyde to obtain *O*-acyl amide, which then undergoes nucleophillic attack by the alcoholic solvent (MeOH) to give 1,1′-iminodicarboxylic acid derivative (Scheme 1).[14]



Scheme 1. General reaction mechanism of U-5C-4CR.

Recently, several other groups have utilized a similar protocol to obtain 1,1′-iminodicarboxylic acid derivatives,[15] which were found to be potent inhibitors toward angiotensin converting enzymes and Zn^{2+} containing endopeptidase and occur in naturally occurring crown gall tumors and poisonous mushrooms.[16] They have also been widely used as chiral ligands. Interestingly, the U-5C-4CR is strongly influenced by the nucleophillic solvents used. To the best of our knowledge, only MeOH has been explored as a solvent. Consequently, the respective Ugi products were obtained as methyl esters (Scheme 1).

2. Results and discussion

In our approach to obtain the hitherto unreported class of Ugi peptide adducts, N^{β}-Fmoc-amino alkyl isonitriles have been synthesized following our previous report.[9a] In a short note, carboxy group of N^{β}-Fmoc-amino acids were directly converted to the corresponding isocyanates through established protocol,[9d] which then undergoes DMAP catalyzed formylation with 98% HCOOH. The formamides were then dehydrated using Burgess reagent (Fig. 2).

Considering the successful implementation as well as mechanistic studies of Ugi 5C-4CR, we expected that other nucleophilic solvents (except MeOH) could give rise to a corresponding ester as Ugi product. In an initial study, *N*-Fmoc–Phe-ψ-[CH_2NC] was

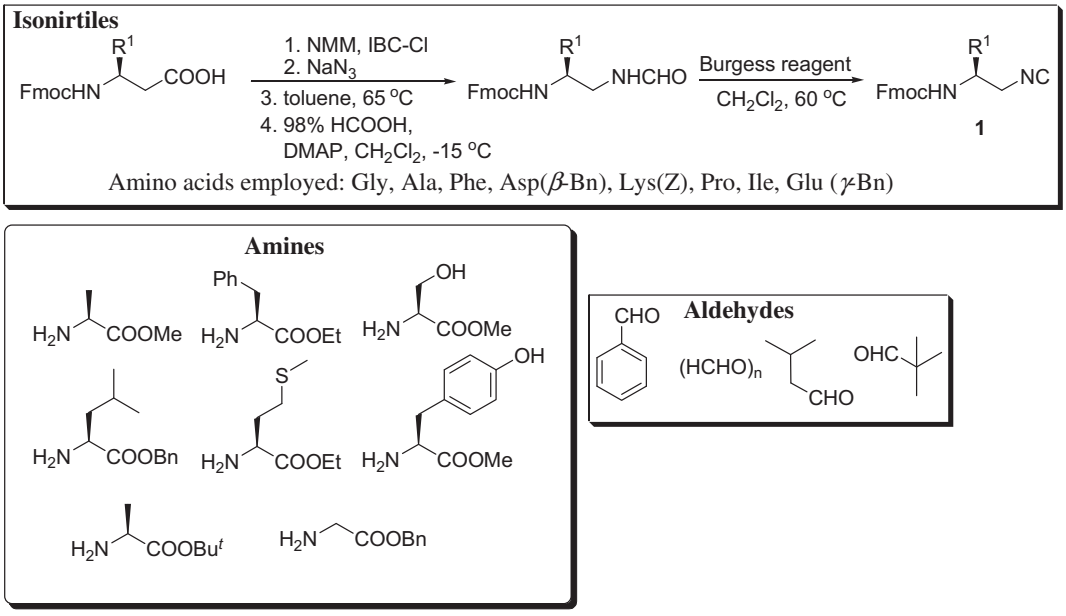
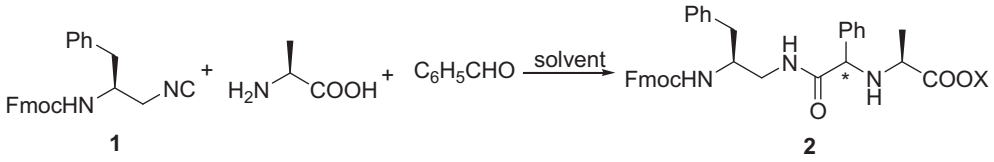


Fig. 2. Building blocks employed for U-4CR.

Focusing on finding a new class of 1,1′-iminodicarboxylated peptidomimetics, we employed N^{β}-Fmoc-protected amino alkyl isonitrile **1b** and amino acid esters. Peptide adducts obtained from present method are rich in chiral centers and possesses both *N*- and *C*-termini. Herein to obtain aforementioned peptidomimetics, we explored U-4CR rather than U-5C-4CR through condensation of amino acid ester, CF_3COOH, isonitrile and aldehyde. The Ugi products **4** were obtained as trifluoroacetamide adducts, which after the cleavage of trifluoroacetyl group from respective adducts affords 1,1′-iminodicarboxylated peptidomimetics **5**. In both the steps a good diastereoselectivity was observed. This work has been demonstrated not only to obtain new class of peptidomimetics, but constitutes an alternative to complement the earlier route of U-5C-4CR involving amino acids providing both amino as well as carboxy termini.

employed in Ugi 5C-4CR (Scheme 2). Enantiopure L-Ala in MeOH was cooled to −30 °C, equimolar amounts of benzaldehyde and *N*-Fmoc–Phe-ψ-[CH_2NC] were added. Indeed, after 46 h of vigorous stirring at 30 °C, we obtained the Ugi product **2** in 59% yield (Table 1, entry a). But only a slight increase in the yield was observed at 60 °C (Table 1, entry b). When the same reaction was performed in presence of EtOH, the desired product was obtained in 28% yield (Table 1, entry c) and only 2% was scaled upon reflux (Table 1, entry d). In contrast, replacing EtOH with benzyl alcohol had no result at room temperature (Table 1, entry e) and about only 5% of the product was obtained at 70 °C (Table 1, entry f). However, the use of *tert*-butanol affords a trace amount of Ugi product at 30 °C as well as at 60 °C (Table 1, entries g and h). These results are in accordance with the known observations that nucleophillic solvents drastically influence the U-5C-4CR. Further, less reactivity of other alcoholic



Scheme 2. Synthesis of **2** via Ugi 5C-3CR using different nucleophillic solvents under various conditions.

Table 1
Results of Ugi 5C-3CR in various solvents from Scheme 2

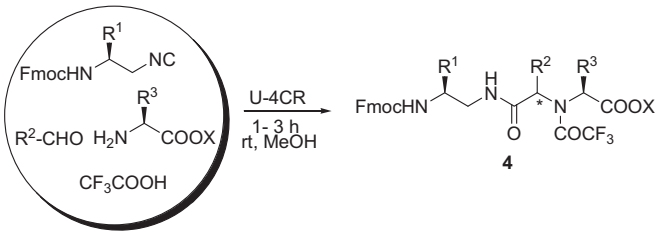
Entry	Solvent[a]	X	Time (h)	Temp (°C)	Yield[b] (%)
a	MeOH	Me	46	30	59
b	MeOH	Me	45	60	61
c	EtOH	Et	58	30	28
d	EtOH	Et	56	70	30
e	BnOH	Bn	58	30	—
f	BnOH	Bn	55	70	05
g	*t*-BuOH	*t*-Bu	50	30	20
h	*t*-BuOH	*t*-Bu	51	60	24

[a] Ten-fold excess of solvents were taken.
[b] Yields of the crude products.

solvents could be expected. This is probably due to steric factors arising from the cyclic intermediate, which restricts the smooth nucleophillic attack by the solvent and poor solubility of the amino acid also.

To circumvent the above drawbacks, it is imperative to choose an alternative protocol. We might expect that a linear peptide-like adduct rather than cyclic intermediate can be obtained easily through U-4CR. While implementing this strategy, selecting strong acid component finds an attractive objective. Thus, trifluoroacetic acid (TFA) was chosen as an acid component in our present study. U-4CR gives linear non cyclic trifluoroacetamide adduct as Ugi product in less duration of time under mild conditions with good diastereoselectivities (Scheme 3). In the subsequent step, the title compounds can be obtained after the removal of trifluoroacetyl function under mild acidic condition (Scheme 4).

To examine the above strategy, a typical reaction has been conducted using H–Ala–OMe as amino component. To a solution of H–Ala–OMe (hydrochloride salt was deprotonated by treatment with Zn dust[17]) in MeOH, an equimolar amount of isovaleraldehyde



Scheme 3. Preparation of 1,1′-iminodicarboxylated peptidomimetics through U-4CR.

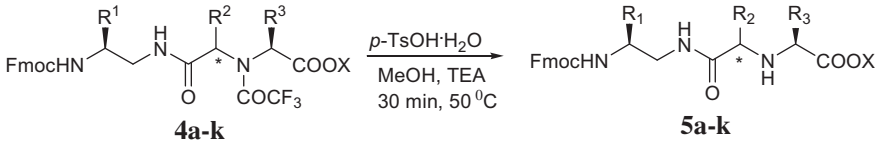
was added at room temperature, the reaction mixture was allowed to stir under the same temperature for 2 h to ensure the imine formation, and then N^{β}-Fmoc–Phe-ψ-[CH_2NC] and trifluoroacetic acid (TFA) were added. After stirring for another 1 h (monitored by TLC analysis), a simple work-up followed by column purification afforded Ugi product **4c** as trifluoroacetamide adduct in good yield (85%, Table 2).

In the final step of the study, we carried out cleavage of trifluoroacetyl group of Ugi products **4**. For the deprotection, the widely known base catalyzed cleavage methods employing K_2CO_3, Na_2CO_3 or NH_3[18] are not compatible with Fmoc chemistry. In pursuit of an alternative protocol, we followed Li et al., approach which involves treatment with *p*-TsOH.[19] This method also facilitates the isolation of product after simple work-up. In the present study (Scheme 3), Ugi products **4** were treated with *p*-TsOH in MeOH at 50 °C, and the final product **5** was formed over 30 min (TLC analysis). A simple work-up led to the isolation of the desired product **5** in good yields (Table 3). However, due to the acidic nature of the reaction conditions employed, about 10–15% of *tert*-butyl ester cleavage was observed in case of **5j** and **5k** (Table 3, entries 10 and 11).

The broad utility of the current version of the strategy to synthesize 1,1′-iminodicarboxylated derivatives is demonstrated by studying the feasibility of the protocol using several functionalized amino acids viz. Ser, Asp(β-Bn), Lys(*Z*), Glu(γ-Bn), Tyr, Cys and Met either as isonitrile or as an amino component. In all the cases Ugi peptide adducts **4** were obtained without any difficulty and products were obtained in good yield within 2–3 h. In addition, we did not observe any considerable decrease in the yield, when we used sterically hindered aldehydes. According to the mechanism of the Ugi-4CR, a mixture of diastereomeric products was obtained, which arises from the new chiral center created at the quaternary carbon of the aldehyde. In addition, both the products **4** and **5** had similar diastereoselectivities and were not separable in column chromatography, although, HPLC had displayed good selectivity of the products.

3. Conclusion

In conclusion, this report outlines the synthesis of 1,1′-iminodicarboxylated peptidomimetics. U-4CR was found to be suitable protocol rather than known U-5C-3CR, provided appropriate acid component was chosen. Reaction of N^{β}-Fmoc-amino alkyl isonitriles, amino acid esters, commercially available aldehydes and trifluoroacetic acid affords trifluoroacetamide peptidomimetic adducts in good yield. Further, cleavage of trifluoroacetyl functionality under mild conditions afforded title molecules. An Ugi 4CR using trifluoroacetic acid as the carboxylic acid component and a performed amino acid ester as the amine component was found to be preferable to the known U-5C-3CR in involving solvolysis of the reaction intermediate.



Scheme 4. Deprotection of trifluoroacetyl group of Ugi products **4**.

Table 2
Trifluoroacetamide possessing Ugi adducts isolated from Scheme 2

Product	R^1	R^2	R^3	X	Yield[a] (%)	Time[b] (h)	dr[c]
4a	H	Ph	CH_2OH	Me	86	1	89:11
4b	CH_3	H	CH_2Ph	Et	91	3	100:0
4c	CH_2Ph	$CH_2CH(CH_3)_2$	CH_3	Me	85	1	79:21
4d	$-(CH_2)_3-$	H	$CH_2CH(CH_3)_2$	Bn	79	2	100:0
4e	CH_2Ph	Ph	CH_3	Me	78	1	84:16
4f	$(CH_2)_4NHZ$	Ph	CH_3	Me	83	2.5	75:25
4g	$CH_2CH(CH_3)_2$	H	CH_2Ph-pOH	Me	89	0.5	100:0
4h	$CH(CH_3)_2$	$C(CH_3)_3$	H	Bn	93	1.5	98:2
4i	CH_2COOBn	H	$CH_2CH_2SCH_3$	Et	87	3	100:0
4j	CH_2CH_2COOBn	$C(CH_3)_3$	CH_3	*t*-Bu	86	1.6	91:9
4k	$CH(CH_3)CH_2CH_3$	$CH_2CH(CH_3)_2$	CH_3	*t*-Bu	88	3.5	97:3

[a] Yields of the isolated product.
[b] Time refers to complete consumption of isonitriles.
[c] Diastereomeric ratios were established by RP-HPLC analysis of the purified products.

4. Experimental

4.1. General

All amino acids aldehydes were used as obtained from Sigma–Aldrich Company, USA. Unless or otherwise mentioned, all amino acids used were of L-configuration. All the solvents were dried and purified using recommended procedures in the literature when necessary. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. IR spectra were recorded on a Schimadzu model FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 300 MHz and 100 MHz spectrometers, respectively. ^{19}F NMR was recorded on a Bruker AMX 376 MHz (internal standard $CFCl_3$). Melting points were determined in an open capillary and are uncorrected. TLC experiments were done using MERCK TLC aluminum sheets (silica gel 60 F_{254}) and chromatograms were visualized by exposing in iodine chamber, UV-lamp or spraying with $KMnO_4$ and heating. Column chromatography was performed on silica gel (100–200 mesh) using ethyl acetate and hexane mixtures as eluent.

4.2. Typical procedure for synthesis of 2

To a solution of H–Ala–OH (5.0 mmol, 445.5 mg) in 50 mL of alcohol (MeOH/EtOH/BnOH/*t*-BuOH) was cooled to −15 °C. *N*-Fmoc–Phe-ψ-[CH_2NC] (5.0 mmol, 1.91 g) and benzaldehyde (5.0 mmol, 0.54 mL) were added. The resulting mixture was stirred at the indicated temperature and time. The mixture was then concentrated in vacuo and the crude product was analyzed.

4.3. General procedure for the synthesis of 4

The trifluoroacetic acid (5.0 mmol, 0.683 mL), amino acid ester (5.1 mmol), and aldehyde (5.1 mmol) were dissolved in MeOH to an approximate concentration of 1 M each. This solution was then stirred for 20 min at room temperature, and then N^{β}-Fmoc-amino alkyl isonitrile (5.0 mmol) was added in one portion. The resulting solution was allowed to stir at room temperature for 4 h. When the reaction was complete by TLC (10% MeOH in CH_2Cl_2), the solvent was removed in vacuo, and the residue purified by column chromatography.

Note: The spectral characterization data for the compounds **4a**–**k** and **5a**–**k** corresponding to the major diastereoisomer.

*4.3.1. Methyl 2-((2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)ethylamino)-2-oxo-1-phenylethyl)-2,2,2-trifluoroacetamido)-3-hydroxypropanoate (**4a**).* White solid; mp 138–139 °C; R_f 0.54 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 21.1, 21.6 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +25.3 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3025, 2877, 2568, 1751, 1735, 1635, 1380 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (br s, 1H, O*H* Ser), 3.15 (t, *J*=2.9 Hz, 2H, NHC*H*$_2$CH$_2$), 3.26 (t, *J*=4.8 Hz, 2H, NHCH$_2$C*H*$_2$), 3.65 (s, 3H, OC*H*$_3$), 3.89–4.01 (m, 2H, C*H*$_2$ Ser), 4.42 (t, *J*=5.8 Hz, 1H, C*H* Fmoc), 4.65 (d, *J*=3.6 Hz, 2H, C*H*$_2$ Fmoc), 4.51 (m, 1H, C*H* Ser), 5.18 (br, 1H, –N*H*), 5.32 (s, 1H, C*H* Ph), 5.83 (br, 1H, N*H*), 7.09–7.48 (m, 13H, *H*Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.6, 39.1, 46.2, 50.5, 55.3, 57.4, 57.6, 65.8, 112.6, 124.6, 125.9, 127.2, 127.8, 128.0, 128.2, 128.9, 129.0, 135.4, 141.0, 142.6, 154.8, 155.6, 168.2, 170.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.44 (s, 3F, COC*F*$_3$); HRMS (ESI) calcd for $C_{31}H_{30}F_3N_3O_7$ *m*/*z* 636.1934 $(M+Na)^+$, found 636.1912.

*4.3.2. Ethyl 2-(N-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)propylamino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-3-phenylpropanoate (**4b**).* Pale yellow solid; mp 143–144 °C; R_f 0.48 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 22.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +54.6 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3030, 2858, 1755, 1741, 1640, 1311 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, *J*=5.6 Hz, 3H, C*H*$_3$ Ala), 1.21 (t, *J*=9.1 Hz, 3H, OCH$_2$C*H*$_3$), 2.96–3.08 (m, 2H, C*H*$_2$ Phe), 3.11–3.23 (m, 2H, CHC*H*$_2$NH), 3.96 (s, 2H, NHCOC*H*$_2$N), 4.11 (m, 2H, OC*H*$_2$CH$_3$), 4.21 (m, 1H, C*H* Ala), 4.42 (t, *J*=3.9 Hz, 1H, C*H* Fmoc), 4.65 (d, *J*=4.7 Hz, 2H, C*H*$_2$ Fmoc), 4.72 (m, 1H, C*H* Phe), 5.65 (br, 1H, N*H*), 5.94 (br, 1H, N*H*), 7.11–7.54 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 17.6, 36.2, 45.9, 46.1, 47.3, 49.5, 52.6, 60.4, 67.0, 112.6, 124.8, 124.6, 126.0, 126.8, 127.3, 127.8, 128.3, 138.4, 141.1, 143.2, 154.8, 155.0, 169.4, 170.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.37 (s, 3F, COC*F*$_3$); HRMS (ESI) calcd for $C_{33}H_{34}F_3N_3O_6$ *m*/*z* 648.2297 $(M+Na)^+$, found 648.2274.

*4.3.3. Methyl 2-(N-(1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropylamino)-4-methyl-1-oxopentan-2-yl)-2,2,2-trifluoroacetamido)propanoate (**4c**).* White solid; mp 123–124 °C; R_f 0.61 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 19.6, 19.8 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +34.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3039, 2860, 1755, 1734, 1711, 1639, 1366 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 [d, *J*=3.9 Hz, 6H, CH(C*H*$_3$)$_2$], 1.42 (d, *J*=7.1 Hz, 3H, C*H*$_3$ Ala), 1.56 [m, 1H, CH$_2$C*H*(CH$_3$)$_2$], 1.87 [m, 2H, C*H*$_2$CH(CH$_3$)$_2$], 2.32–2.41 (m, 2H, C*H*$_2$ Phe), 3.11–3.19 (m, 2H, CHC*H*$_2$), 3.62 (s, 3H, OC*H*$_3$), 4.23 (t, *J*=5.6 Hz, 1H, C*H* Fmoc), 4.31–4.48 (m, 3H, C*H* *i*-Bu, C*H* Ala, C*H* Phe), 4.58 (d, *J*=3.8 Hz, 2H, C*H*$_2$ Fmoc), 5.13 (br, 1H, N*H*), 5.92 (br, 1H, N*H*), 7.10–7.52 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 19.6, 20.4, 37.6, 39.1, 43.0, 45.6, 46.8, 48.1, 50.1, 52.2, 65.6, 112.3, 125.8, 126.2, 127.1, 127.5, 127.9, 128.3, 128.5, 137.3, 141.6, 143.0, 153.2, 155.0, 169.8, 170.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.13 (s, 3F, COC*F*$_3$); HRMS (ESI) calcd for $C_{36}H_{40}F_3N_3O_6$ *m*/*z* 690.2767 $(M+Na)^+$, found 690.2750.

Table 3
1,1′-Iminodicarboxylated peptidomimetics **5** synthesized

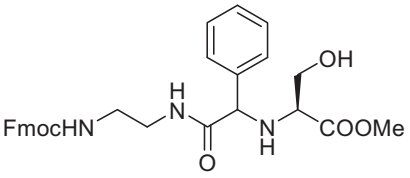
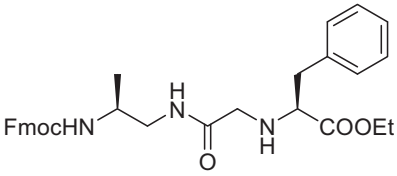
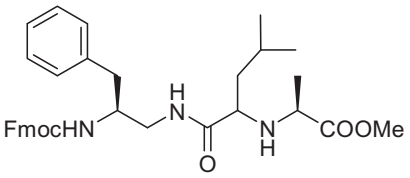
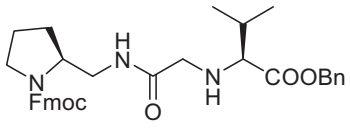
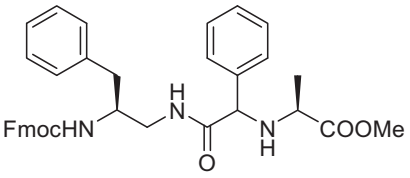
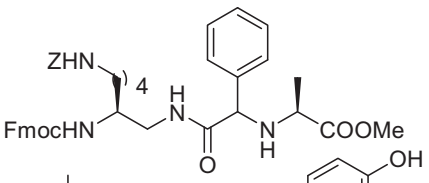
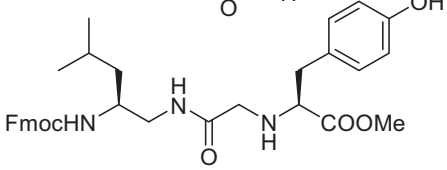
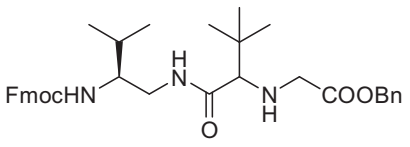
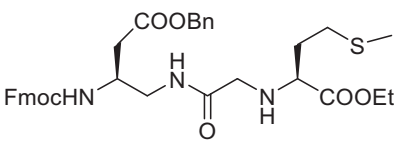
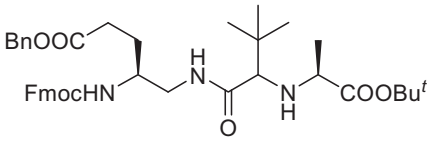
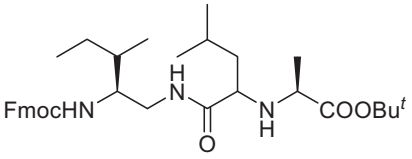
Entry	Product **5**	Structure	Yield[a] (%)	dr[b]	Mp (°C)
1	**5a**		95	88:12	128–130
2	**5b**		91	100:0	141–143
3	**5c**		88	77:23	158–160
4	**5d**		90	100:0	109–111
5	**5e**		88	88:12	135–137
6	**5f**		91	96:4	171–173
7	**5g**		93	100:0	166–168
8	**5h**		95	91:9	98–100
9	**5i**		89	100:0	113–115

Table 3 (*continued*)

Entry	Product **5**	Structure	Yield[a] (%)	dr[b]	Mp (°C)
10	**5j**		76	95:5	160–162
11	**5k**		61	96:4	125–127

[a] Isolated yield after column purification.
[b] Diastereomeric ratios were determined by RP-HPLC analysis of the purified products.

*4.3.4. (9H-Fluoren-9-yl)methyl 2-((2-(N-(1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)-2,2,2-trifluoroacetamido)acetamido)methyl)pyrrolidine-1-carboxylate (**4d**).* White solid; mp 181–183 °C; R_f 0.11 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 20.1 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +79.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2859, 1751, 1742, 1710, 1685, 1631, 1399 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 [d, *J*=4.6 Hz, 6H, $(CH_3)_2$ Val], 1.32–1.38 (m, 2H, NCHCH_2 Pro), 1.41–1.51 (m, 2H, $-NCH_2CH_2$ Pro), 3.12–3.26 [m, 4H, NCH_2CH_2 (Pro), $CHCH_2$], 3.82 (m, 1H, $-NCHCH_2$, Pro), 3.96 (s, 2H, NHCOCH_2N), 4.16 (d, *J*=6.9 Hz, 1H, C*H* Val), 4.42 (t, *J*=8.1 Hz, 1H, C*H* Fmoc), 4.59 (d, *J*=4.6 Hz, 2H, CH_2 Fmoc), 5.14 (s, 2H, OCH_2Ph), 5.65 (br, 1H, $-NH$), 7.12–7.39 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 22.8, 26.7, 28.6, 40.2, 45.5, 46.2, 50.0, 55.1, 65.1, 66.1, 66.8, 112.3, 125.9, 126.8, 127.2, 127.5, 128.0, 128.3, 128.9, 139.1, 140.2, 142.2, 154.1, 155.6, 170.0, 170.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.38 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{36}H_{38}F_3N_3O_6$ *m*/*z* 688.2610 $(M+Na)^+$, found 688.2604.

*4.3.5. Methyl 2-(N-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropylamino)-2-oxo-1-phenylethyl)-2,2,2-trifluoroacetamido) propanoate (**4e**).* Pale yellow solid; mp 151–152 °C; R_f 0.58 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R=23.2, 23.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +82.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3038, 2855, 1750, 1739, 1716, 1645, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, *J*=5.8 Hz, 3H, CH_3 Ala), 2.36–2.48 (m, 2H, CH_2 Phe), 3.11–3.23 (m, 2H, CHCH_2NH), 3.68 (s, 3H, OCH_3), 4.31 (t, *J*=7.6 Hz, 1H, C*H* Fmoc), 4.43 (m, 1H, C*H* Ala), 4.55 (m, 1H, C*H* Phe) 4.67 (d, *J*=6.8 Hz, 2H, CH_2 Fmoc), 5.31 (m, 1H, C*H* Ph), 5.65 (br, 1H, N*H*), 5.91 (br, 1H, N*H*), 7.10–7.48 (m, 18H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 38.6, 43.2, 44.6, 46.1, 50.1, 52.6, 57.2, 66.8, 112.0, 124.8, 125.6, 126.4, 126.8, 127.1, 127.5, 128.0, 128.5, 128.9, 129.0, 135.2, 137.1, 141.0, 143.2, 154.5, 154.8, 167.2, 170.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.91 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{38}H_{36}F_3N_3O_6$ *m*/*z* 710.2454 $(M+Na)^+$, found 710.2441.

*4.3.6. Methyl 2-(N-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-6-(benzyloxycarbonyl)hexylamino)-2-oxo-1-phenylethyl)-2,2,2-trifluoroacetamido)propanoate (**4f**).* White solid; mp 171–172 °C; R_f 0.21 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 18.5, 18.8 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +51.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3020, 2877, 1755, 1745, 1715, 1641, 1369 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11–1.15 (m, 2H, NHCHCH_2CH$_2$ Lys), 1.21 (d, *J*=3.9 Hz, 3H, CH_3 Ala), 1.41–1.49 (m, 4H, $CH_2CH_2CH_2CH_2$ Lys), 2.78 (t, *J*=9.1 Hz, 2H, CH_2 NHZ), 3.09–3.19 (m, 2H, CHCH_2NH–), 3.64 (s, 3H, $-OCH_3$), 3.98–4.11 (m, 2H, C*H* Lys, Ala), 4.38 (t, *J*=5.9 Hz, 1H, C*H* Fmoc), 4.62 (d, *J*=2.9 Hz, 2H, C*H* Fmoc), 5.18 (s, 2H, CH_2 Z), 5.22 (m, 1H, C*H* Ph), 5.81 (br, 1H, N*H*), 6.12 (br, 1H, N*H*), 7.12–7.59 (m, 18H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 19.8, 29.4, 31.2, 39.6, 43.2, 45.8, 45.9, 50.6, 51.1, 57.4, 64.4, 66.1, 112.1, 119.1, 125.4, 126.8, 127.0, 127.5, 127.8, 128.0, 128.3, 128.8, 129.0, 135.4, 139.2, 141.2, 142.9, 153.2, 153.9, 154.5, 168.4, 170.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.10 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{43}H_{45}F_3N_3O_6$ *m*/*z* 825.3087 $(M+Na)^+$, found 825.3050.

*4.3.7. Methyl 2-(N-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpentylamino)-2-oxoethyl)-2,2,2-trifluoroacetamido)-3-(4-hydroxyphenyl)propanoate (**4g**).* White solid; mp 183–184 °C; R_f 0.46 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 23.9 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −68.5 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3069, 2599, 1745, 1739, 1711, 1635, 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 [d, *J*=5.7 Hz, 6H, $(CH_3)_2$ Leu], 1.37–1.42 (m, 2H, CH_2 Leu), 1.78 (m, 1H, C*H* Leu), 3.08–3.18 (m, 2H, CH_2 Tyr), 3.29–3.41 (m, 2H, CHCH_2NH), 3.67 (s, 3H, OCH_3), 3.96 (s, 2H, NHCOCH_2N), 4.12 (m, 1H, C*H* Tyr), 4.42 (t, *J*=4.9 Hz, 1H, C*H* Fmoc), 4.51 (br, 1H, O*H* Tyr), 4.68 (d, *J*=9.1 Hz, 2H, CH_2 Fmoc), 4.76 (m, 1H, C*H* Leu), 5.29 (br, 1H, N*H*), 5.55 (br, 1H, N*H*), 7.01–7.78 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.5, 32.5, 41.5, 43.0, 46.1, 47.1, 49.5, 50.5, 51.3, 65.9, 112.5, 114.8, 127.2, 127.6, 128.0, 128.3, 129.0, 130.5, 141.2, 143.4, 154.5, 154.9, 170.2, 171.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.51 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{35}H_{38}F_3N_3O_7$ *m*/*z* 692.2560 $(M+Na)^+$, found 692.2542.

*4.3.8. Benzyl 2-(N-(1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylbutylamino)-3,3-dimethyl-1-oxobutan-2-yl)-2,2,2-trifluoroacetamido)acetate (**4h**).* White solid; mp 129–130 °C; R_f 0.51 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 24.4, 24.7 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +58.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3089, 2586, 1750, 1745, 1710, 1631, 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 [d, *J*=4.8 Hz, 6H, $(CH_3)_2$ Val], 0.98 [s, 9H, $(CH_3)_3$ *t*-Bu], 2.12 (m, 1H, C*H* Val), 3.09–3.19 (m, 2H, CHCH_2NH), 3.98 (s, 2H, CH_2 Gly), 4.11 (m, 1H, C*H* Val), 4.44 (t, *J*=4.8 Hz, 1H, C*H* Fmoc), 4.51 (s, 1H, C*H* *t*-Bu), 4.62 (d, *J*=6.1 Hz, 2H, CH_2 Fmoc), 5.11 (s, 2H, OCH_2Ph), 5.67 (br, 1H, N*H*), 5.98 (br, 1H, N*H*), 7.11–7.74 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 23.9, 29.5, 31.4, 41.8, 44.1, 46.5, 57.0, 67.1, 67.9, 70.8, 112.2, 125.8, 126.2, 127.7, 127.9, 128.0, 128.3, 128.9, 139.5, 141.2, 143.0, 154.2, 155.2, 168.2, 170.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.05 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{37}H_{42}F_3N_3O_6$ *m*/*z* 704.2923 $(M+Na)^+$, found 704.2904.

*4.3.9. Benzyl-3-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-(2-(2,2,2-trifluoro-N-(1-methoxy-4-(methylthio)-1-oxobutan-2-yl)acetamido) acetamido)butanoate (**4i**).* White solid; mp 111–113 °C; R_f 0.47 (*n*-

hexane/EtOAc, 2:1); RP-HPLC t_R 20.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −24.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3059, 2599, 1755, 1743, 1711, 1632, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J*=4.5 Hz, 3H, OCH_2CH_3), 1.92 (s, 3H, SCH_3), 2.04–2.09 (m, 2H, $CH_2CH_2SCH_3$), 2.17 (t, *J*=3.1 Hz, 2H, $CH_2CH_2SCH_3$), 2.28–2.37 (m, 2H, CH_2 Asp), 3.12–3.22 (m, 2H, $CHCH_2NH$), 4.01 (s, 2H, $NHCOCH_2N$), 4.09 (m, 2H, OCH_2CH_3), 4.28 (t, *J*=6.8 Hz, 1H, C*H* Fmoc), 4.43 (t, *J*=6.4 Hz, 1H, C*H* Met), 4.61 (d, *J*=8.6 Hz, 2H), 4.72 (m, 1H, C*H* Asp), 5.16 (s, 2H, OCH_2Ph), 5.67 (br, 1H, N*H*), 5.91 (br, 1H, N*H*), 7.08–7.79 (m, 13H, *H*Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 16.1, 26.9, 29.2, 38.0, 41.2, 46.3, 49.9, 50.3, 58.7, 60.0, 66.5, 67.3, 112.0, 121.4, 125.8, 127.5, 127.9, 128.0, 128.5, 128.9, 139.4, 141.2, 143.6, 154.5, 154.9, 170.2, 170.9, 171.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.79 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{37}H_{40}F_3N_3O_8S$ *m*/*z* 766.2386 $(M+Na)^+$, found 766.2355.

*4.3.10. Benzyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-(2-(N-(1-tert-butoxy-1-oxopropan-2-yl)-2,2,2-trifluoroacetamido)-3,3-dimethylbutanamido)pentanoate (**4j**).* White solid; mp 92–93 °C; R_f 0.61 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 20.0, 20.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −8.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3065, 2859, 1752, 1738, 1710, 1640, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 [s, 9H, $(CH_3)_3$ *t*-Bu], 1.34 [s, 9H, $O(CH_3)_3$], 1.39 (d, *J*=11.2 Hz, 3H, CH_3 Ala), 1.73–1.79 (m, 2H, CH_2CH_2COO), 2.09 (t, *J*=11.6 Hz, 2H, CH_2CH_2COO), 3.12–3.19 (m, 2H, $CHCH_2NH$), 3.96 (m, 1H, C*H* Ala), 4.42 (t, *J*=5.6 Hz, 1H, C*H* Fmoc), 4.47 (m, 1H, C*H* *t*-Bu), 4.52 (m, 1H, C*H* Glu), 4.68 (d, *J*=3.9 Hz, 2H, CH_2 Fmoc), 5.21 (s, 2H, OCH_2Ph), 5.68 (br, 1H, N*H*), 6.15 (br, 1H, N*H*), 7.16–7.79 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.4, 26.5, 27.0, 27.9, 33.4, 44.5, 46.1, 46.9, 49.7, 66.9, 67.0, 68.5, 81.4, 112.8, 125.6, 126.4, 126.8, 127.8, 127.9, 128.2, 128.5, 139.8, 141.7, 143.2, 153.6, 154.0, 169.9, 170.2, 171.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.29 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{42}H_{50}F_3N_3O_8$ *m*/*z* 804.3448 $(M+Na)^+$, found 804.34421.

*4.3.11. tert-Butyl 2-(N-(1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylpentylamino)-4-methyl-1-oxopentan-2-yl)-2,2,2-trifluoroacetamido)propanoate (**4k**).* White solid; mp 120–123 °C; R_f 0.63 (*n*-hexane/EtOAc, 2:1); RP-HPLC t_R 20.0, 20.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +120.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3089, 2577, 1750, 1742, 1725, 1630, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=4.8 Hz, 3H, $CH_3CHCH_2CH_3$ Ile), 0.94 [d, *J*=5.6 Hz, 6H, $(CH_3)_2$ *i*-Pr], 1.01 (d, *J*=11.2 Hz, 3H, $CH_3CHCH_2CH_3$ Ile), 1.11–1.19 (m, 2H, CH_2 Ile), 1.32 [s, 9H, $O(CH_3)_3$], 1.41 (d, *J*=5.4 Hz, 3H, CH_3 Ala), 1.51–1.62 (m, 3H, CH_2 *i*-Bu, C*H* *i*-Pr), 2.11 (m, 1H, $CHCH_3$ Ile), 3.12–3.19 (m ,2H, $CHCH_2NH$), 4.04 (m, 1H, C*H* Ile), 4.43 [m, 1H, C*H*(*i*-Bu)], 4.58–4.61 (m, 2H, C*H* Fmoc, C*H* Ala), 4.64 (d, *J*=5.5 Hz, 2H, CH_2, Fmoc), 5.55 (br, 1H, N*H*), 6.13 (br, 1H, N*H*), 7.21–7.85 (m, 8H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 14.0, 14.9, 21.4, 21.8, 24.6, 27.8, 37.6, 38.1, 41.1, 46.7, 47.0, 48.5, 55.0, 64.8, 81.4, 113.4, 126.7, 127.9, 128.4, 128.8, 139.8, 141.1, 143.2, 153.6, 154.0, 170.4, 171.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.69 (s, 3F, $COCF_3$); HRMS (ESI) calcd for $C_{36}H_{48}F_3N_3O_6$ *m*/*z* 698.3319 $(M+Na)^+$, found 698.3311.

4.4. General procedure for the synthesis of 5

Trifluoroacetamide Ugi product **4** (5.0 mmol) was dissolved in MeOH (8.0 mL), *p*-TsOH·H_2O (5.5 mmol, 1.045 g) was added and the resulting solution was refluxed at 50 °C for 30 min. The reaction mixture was then cooled to room temperature, TEA (5.5 mmol, 0.56 mL) was added, and stirring was continued for another 5 min to neutralize the tosylate salt. The solvent was removed in vacuo and the residue was purified by column chromatography.

*4.4.1. (2S)-Methyl 2-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)ethylamino)-2-oxo-1-phenylethylamino)-3-hydroxypropanoate (**5a**).* White solid; mp 128–139 °C; R_f 0.30 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 8.2, 8.8 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +3.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3054, 2875, 1741, 1738, 1659, 1588, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (br, 1H, O*H* Ser), 3.26–3.32 (m, 2H, $NHCH_2CH_2$), 3.41–3.49 (m, 2H, $NHCH_2CH_2$), 3.57 (m, 1H, C*H* Ser), 3.71 (s, 3H, OCH_3), 3.86 (m, 1H, CH_2 Ser), 4.00 (m, 1H, CH_2 Ser), 4.43 (t, *J*=7.2 Hz, 1H, C*H* Fmoc), 4.65 (d, *J*=8.6 Hz, 2H, CH_2 Fmoc), 4.88 (m, 1H, C*H*(Ph)), 5.92 (br, 1H, N*H*), 6.68 (br, 2H, N*H*), 7.06–7.76 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.1, 43.4, 46.6, 52.3, 60.0, 62.4, 66.9, 72.1, 126.3, 126.9, 128.2, 128.4, 128.7, 129.2, 129.5, 135.5, 141.2, 143.6, 155.8, 169.9, 170.7; HRMS (ESI) calcd for $C_{29}H_{31}N_3O_6$ *m*/*z* 540.2111 $(M+Na)^+$, found 540.2118.

*4.4.2. (S)-Ethyl 2-(2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)propylamino)-2-oxoethylamino)-3-phenylpropanoate (**5b**).* White solid; mp 141–143 °C; R_f 0.18 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 7.5 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −18.6 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3050, 2864, 1740, 1735, 1631, 1511, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 6H, CH_3 Ala, OCH_2CH_3), 2.92 (m, 1H, CH_2 Phe), 3.12 (m, 1H, CH_2 Phe), 3.29 (m, 1H, $CHCH_2NH$), 3.38–3.44 (m, 4H, $CHCH_2NH$, $COCH_2NH$), 3.69 (m, 1H, C*H* Phe), 4.03 (m, 2H, OCH_2CH_3), 4.21 (m, 1H, C*H* Ala), 4.44 (t, *J*=7.4 Hz, 1H, C*H* Fmoc), 4.68 (d, *J*=8.6 Hz, 2H, CH_2 Fmoc), 5.81 (br, 1H, N*H*), 6.73 (br, 2H, N*H*), 7.06–7.78 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 17.8, 35.2, 45.3, 46.1, 46.9, 48.7, 57.3, 59.2, 66.4, 125.8, 126.3, 126.9, 127.3, 127.6, 127.9, 128.4, 139.8, 140.9, 143.2, 155.1, 170.2, 170.9; HRMS calcd for $C_{31}H_{35}N_3O_5$ *m*/*z* 552.2474 $(M+Na)^+$, found 552.2481.

*4.4.3. (S)-Methyl 2-(1-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropylamino)-4-methyl-1-oxopentan-2-ylamino)propanoate (**5c**).* White solid; mp 158–160 °C; R_f 0.18 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 9.8, 10.4 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +113.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3040, 2898, 1758, 1721, 1641, 1575, 1388 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 [d, *J*=5.6 Hz, 6H, $CH(CH_3)_2$], 1.24 (d, *J*=6.8 Hz, 3H, CH_3 Ala), 1.57 [m, 2H, $CH_2CH(CH_3)_2$], 1.78 [m, 1H, $CH_2CH(CH_3)_2$], 2.92 (m, 1H, CH_2 Phe), 3.03 (m, 1H, CH_2 Phe), 3.21 (m, 1H, $CHCH_2$), 3.37 (m, 1H, $CHCH_2$), 3.58–3.68 (m, 2H, C*H* *i*-Bu, C*H* Ala), 3.71 (s, 3H, OCH_3), 4.41 (t, *J*=7.7 Hz, 1H, C*H* Fmoc), 4.52 (m, 1H, C*H* Phe), 4.67 (d, *J*=8.1 Hz, 2H, CH_2 Fmoc), 5.78 (br, 2H, N*H*), 6.41 (br, 1H, N*H*), 7.08–7.81 (m, 13H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 19.2, 20.1, 38.6, 39.6, 42.3, 46.2, 52.1, 52.8, 53.9, 55.7, 66.3, 125.3, 126.4, 127.8, 128.1, 128.5, 128.9, 136.2, 140.2, 143.1, 156.3, 170.2, 170.8; HRMS (ESI) calcd for $C_{34}H_{41}N_3O_5$ *m*/*z* 594.2944 $(M+Na)^+$, found 594.2946.

*4.4.4. (S)-(9H-Fluoren-9-yl)methyl 2-((2-((S)-1-(benzyloxy)-3-methyl-1-oxobutan-2-ylamino)acetamido)methyl)pyrrolidine-1-carboxylate (**5d**).* Pale yellow solid; mp 109–111 °C; R_f 0.21 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 6.9 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −89.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3048, 2879, 1740, 1731, 1660, 1551, 1386 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.98 [d, *J*=5.2 Hz, 6H, $(CH_3)_2$ Val], 1.28–1.60 (m, 4H, $NCH_2CH_2CH_2$ Pro), 2.56 (m, 1H, $CH(CH_3)_2$ Val), 3.28–3.49 (m, 7H, NCH_2 Pro, $NCHCH_2$ Pro, $COCH_2NH$, C*H* Val), 3.80 (m, 1H, N*CH* Pro), 4.41 (t, *J*=7.1 Hz, 1H, C*H* Fmoc), 4.68 (d, *J*=8.8 Hz, 2H, CH_2 Fmoc), 5.12 (s, 2H, OCH_2Ph), 6.32 (br, 1H, N*H*), 6.79 (br, 1H, N*H*), 7.16 (s, 5H, Ar*H*), 7.31–7.83 (m, 8H, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 21.0, 26.2, 29.8, 42.1, 46.3, 47.2, 49.8, 55.2, 59.8, 64.2, 66.9, 126.4, 126.9, 127.2, 127.5, 128.0, 128.2, 128.6, 141.0, 141.6, 143.2, 155.8, 169.9, 170.3; HRMS (ESI) calcd for $C_{34}H_{39}N_3O_5$ *m*/*z* 592.2787 $(M+Na)^+$, found 592.2796.

*4.4.5. (S)-Methyl 2-(2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenylpropylamino)-2-oxo-1-phenylethylamino)propanoate (**5e**).* Pale yellow solid; mp 135–137 °C; R_f 0.41 ($CHCl_3$/MeOH, 8:2); RP-HPLC: t_R 11.2, 11.5 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +69.8 (*c* 1.0,

$CHCl_3$); IR (KBr) ν_{max} 3048, 2881, 1742, 1736, 1660, 1581, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J=8.6 Hz, 3H, CH_3 Ala), 2.92 (m, 1H, CH_2 Phe), 3.03 (m, 1H, CH_2 Phe), 3.26 (m, 2H, CHCH_2NH), 3.34–3.42 (m, 2H, CHCH$_2$NH, CH Ala), 3.68 (s, 3H, OCH_3), 4.41 (t, J=7.9 Hz, 1H, CH Fmoc), 4.58 (m, 1H, CH Phe), 4.67 (d, J=6.8 Hz, 2H, CH_2 Fmoc), 4.71 (s, 1H, CH Ph), 5.98 (br, 2H, NH), 6.63 (br, 1H, NH), 7.04–7.80 (m, 18H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 39.6, 42.4, 44.8, 52.1, 52.9, 53.7, 6.09, 66.7, 126.0, 126.4, 127.4, 127.6, 127.8, 128.2, 128.3, 128.4, 128.6, 128.8, 138.2, 139.6, 140.8, 143.1, 155.6, 169.8, 170.2; HRMS (ESI) calcd for $C_{36}H_{37}N_3O_5$ m/z 614.2631 $(M+Na)^+$, found 614.2638.

*4.4.6. (2S)-Methyl 2-(2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-6-(benzyloxycarbonyl) hexylamino)-2-oxo-1-phenylethylamino)propanoate (**5f**).* White solid; mp 171–173 °C; R_f 0.17 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 5.6, 5.9 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −109.7 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3051, 2870, 1739, 1735, 1655, 1589, 1390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=5.5 Hz, 3H, CH_3 Ala) 1.28–1.45 [m, 6H, NHCH$_2$(CH_2)$_3$ Lys], 2.44 [m, 2H, NHCH_2(CH$_2$)$_3$ Lys], 3.26 (m, 1H, NHCHCH_2NH), 3.59 (m, 2H, NHCHCH_2NH, CH Ala), 3.69 (s, 3H, OCH_3), 4.44 (m, 2H, CH Fmoc, CH Lys) 4.65 (d, J=7.0 Hz, 2H, CH_2 Fmoc), 4.78 (m, 1H, CH Ph), 5.08 (s, 2H, CH$_2$ Z), 5.74 (br, 2H, NH), 6.64 (br, 1H, NH), 7.08–7.79 (m, 18H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.2, 27.7, 29.1, 40.3, 46.5, 47.2, 47.8, 52.3, 54.3, 59.6, 61.2, 66.8, 119.7, 124.9, 125.3, 126.8, 127.5, 127.7, 127.9, 128.3, 128.9, 129.4, 139.2, 140.2, 141.1, 143.6, 155.7, 156.4, 170.1, 171.3; HRMS (ESI) calcd for $C_{41}H_{46}N_4O_7$ m/z 729.3264 $(M+Na)^+$, found 729.3270.

*4.4.7. (S)-Methyl 2-(2-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methylpentylamino)-2-oxoethylamino)-3-(4-hydroxyphenyl)propanoate (**5g**).* White solid; mp 166–168 °C; R_f 0.11 ($CHCl_3$/MeOH, 8:2); RP-HPLC: t_R 5.2 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −29.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3038, 2868, 1742, 1736, 1655, 1538, 1394 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 [d, J=4.2 Hz, 6H, (CH_3)$_2$ Leu], 1.37 (m, 2H, CH_2 Leu), 1.76 (m, 1H, CH Leu), 2.97 (m, 1H, CH_2 Tyr), 3.13 (m, 1H, CH_2 Tyr), 3.28 (m, 1H, CHCH_2NH), 3.41 (s, 2H, COCH_2NH), 3.47 (m, 1H, CHCH_2NH), 3.71 (s, 3H, OCH_3), 3.79 (m, 1H, CH Tyr), 3.99 (m, 1H, CH Leu), 4.43 (t, J=7.0 Hz, 1H, CH Fmoc), 4.68 (d, J=78.1 Hz, 2H, CH_2 Fmoc), 4.98 (br, 1H, OH Tyr), 5.97 (br, 2H, NH), 6.61 (br, 1H, NH), 6.76 (d, J=7.2 Hz, 2H, ArH), 6.93 (d, J=7.1 Hz, 2H, ArH), 7.31–7.79 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 22.6, 35.3, 40.7, 42.1, 46.2, 47.4, 49.6, 52.1, 58.3, 65.4, 115.6, 126.6, 128.0, 128.2, 128.7, 129.0, 131.2, 141.1, 143.2, 155.9, 156.3, 170.3, 173.8; HRMS calcd for $C_{33}H_{39}N_3O_6$ m/z 596.2737 $(M+Na)^+$, found 596.2748.

*4.4.8. Benzyl 2-(1-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylbutylamino)-3,3-dimethyl-1-oxobutan-2-ylamino)acetate (**5h**).* White solid; mp 98–100 °C; R_f 0.46 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 12.4, 12.9 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +74.5 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3048, 2868, 1745, 1740, 1664, 1579, 1389 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 [d, J=4.8 Hz, 6H, (CH_3)$_2$ Val], 1.08 [s, 9H, (CH_3)$_3$ *t*-Bu], 2.38 (m, 1H, CH Val), 3.22 (m, 1H, CHCH_2NH), 3.37–3.50 (m, 4H, CHCH_2NH, CH *t*-Bu, CH_2 Gly), 4.18 (m, 1H, CH Val), 4.41 (t, J=7.0 Hz, 1H, CH Fmoc), 4.68 (d, J=7.5 Hz, 2H, CH_2 Fmoc), 5.12 (s, 2H, OCH_2Ph), 5.49 (br, 1H, NH), 6.18 (br, 2H, NH), 7.15 (s, 5H, *H*Ar), 7.26–7.35 (m, 4H, ArH), 7.54 (d, J=6.9 Hz, 2H, ArH), 7.76 (d, J=7.0 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 23.8, 29.6, 35.2, 42.3, 46.8, 47.1, 57.8, 66.1, 67.3, 74.8, 126.2, 126.8, 127.3, 127.6, 128.0, 128.4, 128.8, 141.0, 141.3, 143.5, 155.6, 169.3, 170.1; HRMS (ESI) calcd for $C_{35}H_{43}N_3O_5$ m/z 608.3100 $(M+Na)^+$, found 608.3113.

*4.4.9. (S) Benzyl-3-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-(2-((S)-1-methoxy-4-(methylthio)-1-oxobutan-2-ylamino)acetamido)butanoate (**5i**).* Pale yellow solid; mp 113–115 °C; R_f 0.58 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 13.1, 13.8 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ +28.9 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3048, 2865, 1745, 1740, 1732, 1654, 1555, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J=6.6 Hz, 3H, OCH$_2$CH_3), 2.01 (s, 3H, SCH_3), 2.12 (m, 2H, CH_2CH$_2$SCH$_3$), 2.38 (m, 3H, CH$_2$CH_2SCH$_3$, CH_2 Asp), 2.51 (m, 1H, CH_2 Asp), 3.32–3.51 (m, 5H, CHCH_2NH, COCH_2NH, CH Met), 4.09 (m, 2H, OCH_2CH$_3$), 4.44 (t, J=7.0 Hz, 1H, CH Fmoc), 4.67 (d, J=8.2 Hz, 2H, CH_2 Fmoc), 4.74 (m, 1H, CH Asp), 5.10 (s, 2H, OCH_2Ph), 5.71 (br, 1H, NH), 5.96 (br, 1H, NH), 6.43 (br, 1H, NH), 7.16 (s, 5H, ArH), 7.25–7.78 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 16.9, 29.8, 31.0, 38.4, 44.2, 46.3, 50.2, 51.1, 57.9, 59.8, 66.9, 67.5, 126.5, 126.9, 127.4, 127.9, 128.2, 128.6, 128.9, 141.0, 141.3, 143.5, 155.8, 169.8, 170.1, 172.3; HRMS calcd for $C_{35}H_{41}N_3O_7S$ m/z 670.2563 $(M+Na)^+$, found 670.2571.

*4.4.10. (S)-Benzyl 4-(((9H-fluoren-9-yl)methoxy)carbonyl)-5-(2-((S)-1-tert-butoxy-1-oxopropan-2-ylamino)-3,3-dimethylbutanamido) pentanoate (**5j**).* White solid; mp 160–162 °C; R_f 0.55 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 9.1, 9.7 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −24.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3051, 2855, 1751, 1745, 1738, 1655, 1540, 1369 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 [s, 9H, (CH_3)$_3$ *t*-Bu], 1.23 (d, J=6.8 Hz, 3H, CH_3 Ala), 1.38 [s, 9H, O(CH_3)$_3$], 1.78 (m, 2H, CH_2CH$_2$COO), 2.13 (t, J=6.1 Hz, 2H, CH$_2$CH_2COO), 3.23 (m, 1H, CHCH_2NH), 3.29 (m, 1H, CHCH_2NH), 3.61 (s, 1H, CH *t*-Bu), 3.74 (m, 1H, CH Ala), 4.36 (m, 1H, CH Glu), 4.42 (t, J=6.4 Hz, 1H, CH Fmoc), 4.65 (d, J=8.0 Hz, 2H, CH_2 Fmoc), 5.14 (s, 2H, OCH_2Ph), 5.92 (br, 1H, NH), 6.73 (br, 2H, NH), 7.13 (s, 5H, ArH), 7.23–7.35 (m, 4H, ArH), 7.51 (d, J=7.1 Hz, 2H, *H*Ar), 7.75 (d, J=7.2 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.8, 23.8, 25.3, 26.7, 28.9, 36.2, 43.8, 45.7, 49.3, 55.1, 65.6, 67.4, 73.6, 81.2, 126.2, 126.9, 127.2, 127.7, 128.1, 128.4, 128.8, 140.8, 141.2, 143.0, 155.4, 169.2, 170.3, 170.5; HRMS (ESI) calcd for $C_{40}H_{51}N_3O_7$ m/z 708.3625 $(M+Na)^+$, found 708.3629.

*4.4.11. (S)-tert-Butyl 2-(1-((2S,3S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methylpentylamino)-4-methyl-1-oxopentan-2-ylamino) propanoate (**5k**).* White solid; mp 125–127 °C; R_f 0.47 ($CHCl_3$/MeOH, 8:2); RP-HPLC t_R 8.6, 8.9 (60–100% ACN; 30 min); $[\alpha]_D^{20}$ −22.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3048, 2849, 1742, 1740, 1738, 1661, 1538, 1355 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89–1.01 [m, 12H, CH_3CHCH$_2$CH_3 Ile, (CH_3)$_2$ *i*-Pr], 1.31 (m, 5H, CH_3 Ala, CH_2 Ile), 1.37 [s, 9H, O(CH_3)$_3$], 1.49 (m, 2H, CH_2 *i*-Bu), 1.71 (m, 1H, CH *i*-Pr), 2.13 (m, 1H, CHCH$_3$ Ile), 3.27 (m, 1H, CHCH_2NH), 3.32 (m, 1H, CHCH_2NH), 3.58 [m, 1H, CH(*i*-Bu)], 3.74 (m, 1H, CH Ala), 4.33 (m, 1H, CH Ile), 4.43 (t, J=6.6 Hz, 1H, CH Fmoc), 4.63 (d, J=8.2 Hz, 2H, CH_2 Fmoc), 5.67 (br, 1H, NH), 6.69 (br, 2H, NH), 7.21–7.32 (m, 4H, ArH), 7.50 (d, J=7.0 Hz, 2H, ArH), 7.78 (d, J=7.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 14.6, 16.7, 21.4, 23.2, 26.4, 29.1, 37.3, 40.9, 42.1, 48.6, 56.2, 56.4, 58.1, 66.3, 81.8, 125.4, 126.3, 126.7, 127.2, 141.2, 143.4, 155.7, 169.3, 170.2; HRMS (ESI) calcd for $C_{34}H_{49}N_3O_5$ m/z 602.3570 $(M+Na)^+$, found 602.3573.

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